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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,811	05/14/2001	Robert E. Reiter	02307K-141581	9472

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EXAMINER	
REDDIG, PETER J	
ART UNIT	**PAPER NUMBER**
1642	

MAIL DATE	DELIVERY MODE
10/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/854,811	REITER ET AL.	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *June 27, 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53,58-64,70,71,74,78-88,93-97,99 and 100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53, 58-64, 70, 71, 74, 78-88, 93-97, 99 and 100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed June 27, 2008 in response to the Office Action of December 28, 2007 is acknowledged and has been entered. Previously pending claims 67, 77, 91 and 98 have been cancelled and claims 53 and 78 have been amended. Claims 53, 58-64, 70, 71, 74, 78-88, 93-97, 99 and 100 are currently pending and under consideration.

2. The following rejections are being maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 53, 58-64, 70, 71, 74, 78-88, 93-97, 99 and 100 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons previously set forth in the Office Action of December 28, 2007, section 5, pages 2-11.

In the Office Action of December 28, 2007, section 5, pages 2-11, Examiner argued.

Applicants argue that most of the concerns raised in the action relate to the induction of a cellular immune response. One concern raised by the Action is whether the length of the various peptide fragments set forth in the claims were too long to be active in inducing a cellular immune response. In fact, professionally antigen presenting cells such as dendritic cells digest proteins into smaller peptides. In the lymph node, the DC will display these antigenic peptides on its surface by coupling them to MHC Class II molecules. This MHC:antigen complex is then recognized by T cells passing through the lymph node. Exogenous antigens are usually displayed on MHC Class II molecules, which interact with CD4+ helper T cells. CD4+ lymphocytes, or TH, are immune response mediators, and play an important role in establishing and maximizing the capabilities of the adaptive immune response. Thus, the length of a fragment is *no* bar to its suitability in generating such responses. A large fragment can be

processed to provide a number of different subfragments to be presented on the surface of an Antigen Presenting Cell (see Exhibit A, pages 115 to 119 of Roitt et al., *Immunology,* 5th Edition, Mosby press, Philadelphia). Some such fragments will be of a length of sequence suitable for binding to an HLA allele. This comports with the results of Kiessling et al., already of record, who found the presence of $CD8^+$ reactive cells which recognized two of their peptide fragments in the serum of cancer patients *who had not been administered the PSCA peptide fragments.*

Applicants arguments have been carefully considered, but have not been found persuasive because Kiessling et al. does not teach the treatment of any cancer by inducing an immune response with any of the claimed proteins and the peptides taught by Kiessling et al. are not the peptides claimed and it cannot be determined if the claimed proteins will induce an immune response that is effective to treat any of the claimed cancers because it is not known and cannot be predicted if the claimed proteins will be processed and bind MHC molecules so as to be presented in a way that will elicit an immune response that is effective for immunotherapy of cancer which is the clearly the contemplated use of the claimed method. Additionally, there is no teaching that any of the claimed peptides will interact with MHC Class II or class I molecules, which have specific constraints on are their ability to interact with a peptide, see the cited Roitt, thus it cannot be predicted that MHC class II or I will interact with the claimed proteins. Although Kiessling found $CD8^+$ reactive cells in prostate cancer patients that recognized two of their peptide fragments, the presence of these $CD8^+$ reactive cells was not sufficient to ameliorate the prostate cancer as the patients still had prostate cancer.

Applicants argue that a second concern raised in the action is the absence of clinical trials indicating any efficacy of a PSCA peptide vaccine. Thomas-Kaskel et al. have now reported the results of a clinical trial using PSCA14-22 and PSA peptide-loaded dendritic cells to vaccinate advanced prostate cancer patients (see. Thomas-Kaskel et al., Intl. J. Cancer 119:2428-2434 (2006), enclosed with IDS). The study concludes:

> The experience from this trial argues that DC-based vaccination against PSCA in the dose range given seems worthwhile for

> further clinical testing as a vaccination antigen. However, immunosuppression is likely to prevent higher rates of immune responders unless active immunotherapy is being employed earlier in the course of the disease, for example in the setting of a "PSA relapse" after radical prostatectomy. The correlation of immune responses with superior overall survival, further supported by documented regression of lymph node metastasis or impressive subjective pain relief, suggests that tumor-specific cellular immunity may indeed provide clinical benefit in CaP, although the optimal time point and vaccination schedule need further clarification.

These results demonstrate, contrary to the Action, that the *in vitro* observations as to the PSCA peptides *are predictable* in translating to the clinic.

Applicants arguments have been carefully considered, but have not been found persuasive because the teachings of Thomas-Kaskel et al. are not commensurate in scope with the claimed invention as none of the claims are drawn to using peptide-loaded dendritic cells to elicit an immune response and Thomas-Kaskel do not use any of the specifically claimed peptides. Although new claim 98 is drawn to the method of claim 53, wherein dendritic cells are used to present the claimed peptides to T cells in the context of MHC class I and II molecules, claim 98 depends on claim 53 where the PSCA proteins or fragments are administered to a subject directly, thus the claim does not read on administering peptide-loaded dendritic cells to a subject, but the mechanisms of presentation of the administered PSCA peptide.

Applicants argue that moreover, the very existence of such clinical trials strongly evidences that persons of ordinary skill in the art felt the art was reasonably predictable and ought to be so viewed by the Examiner. Indeed, the MPEP §2107.03 at 2100-35 right column provides:

> ... In order to determine a protocol for phase I testing, the first phase of clinical investigation, some credible rationale of how the drug might be effective or could be effective would

> be necessary. Thus, as a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.

Applicants arguments have been carefully considered, but have not been found persuasive because, as set forth above, the teachings of Thomas-Kaskel et al. are not commensurate in scope with the claimed invention as none of the claims are drawn to using peptide-loaded dendritic cells to elicit an immune response and Thomas-Kaskel do not use any of the claimed peptides.

Applicants argue that thirdly, the Examiner cites Kiessling et al. as finding that only 2 of 8 tested peptide fragments bound to the HLA-A-201. Nothing in Kiessling indicates that it took undue experimentation to identify such peptide fragments. They used standard models to identify 8 candidates and found 2 fragments to be active (i.e., PSCA14-22 and PSCA~05_113). This hardly seems to involve undue amount of experimentation. The steps performed are routine and the amount of experimentation required to identify 2 useful agents, simply *minimal* for this field of art. The standard for enablement is not whether *any* experimentation is required but whether the amount of experimentation is undue. That some experimentation may be necessary to identify operative species does not constitute a lack of enablement. As the Federal Circuit has stated, "the key word is 'undue', not 'experimentation' " in determining whether pending claims are enabled. *Wands,* 8 U.S.P.Q.2d at 1405 (Fed. Cir. 1988). Indeed, a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance for practicing the invention.

Applicants arguments have been carefully considered, but have not been found persuasive because the teachings of Kiessling et al. are not commensurate in scope with the claimed because Kiessling et al. do not demonstrate that any immune response to any PSCA fragment is sufficient to treat any of the claimed cancers, as set forth above.

Applicants argue that without doubt, the pharmaceutical arts are one in which it is routine to screen a large number of agents in order to find useful ones. The expenditures of substantial sums to practice an invention is no bar to enablement. Indeed, in the context of dose response, the Federal Circuit held in 1988 that if a specification teaches one embodiment and sets forth a method for determining dose/response, the experimentation required to determine a dose/response curve is not undue, even if the studies proved to cost approximately $50,000 and took 6-12 months to accomplish. *United States v. Telectronics,* 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied,* 490 U.S. 1046 (1988).

Applicants arguments have been carefully considered, but have not been found persuasive because although one of ordinary skill could screen for the proteins that would function as claimed, in particular, screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

Applicants argue that previously, the Applicants cited Matsueda et al. as disclosing that one (i.e., PSCA76-84) of three tested peptides was active. Applicants now enclose with their IDS another Matsueda et al. reference which reports on the finding that two out of an additional 11 PSCA peptides (i.e., PSCA 7-15 and PSCA 21-30) were active (see, Matsueda et al., *Cancer Immunol. Immunother.* 53:479-489 (2004)). Having found them, Matsueda et al. again state that their peptides should be considered for use in clinical trials in immunotherapy. Clearly, persons of ordinary skill in the art are able to repeatedly identify suitable peptide fragments without much experimentation at all and these persons view the obtained peptides as being credible candidates for immunotherapy. The last sentence of Kiessling et al. is in accord on this last point: Our results emphasize the suitability of PSCA target molecule for the immunotherapy of prostate cancer.

Applicants' arguments have been carefully considered, but have not been found persuasive because Matsueda et al. do not use any of the claimed peptides and, although Matsueda et al. showed that two peptides elicited an immune response, Matsueda et al. did not show that the immune response was effective to treat any tumor.

Applicants argue that the invention is in the field of polypeptide vaccine development. This field of art, drug development, is traditionally one in which a large volume of screening is both typical and routine. It is a field in which the courts have held that the necessary showing for enablement does not require testing in humans.

Applicants arguments have been carefully considered, but have not been found persuasive because although one of ordinary skill could screen for the proteins that would function as claimed, in particular, screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention. Although human testing is not required, neither the specification nor the art of record has provided data that is commensurate in scope with the claimed invention so as to enable the claimed invention.

Applicants argue that as set forth in previous papers, the specification provides all the guidance required to practice the invention. Without revisiting earlier remarks, the specification discloses the PSCA protein sequence, methods of identifying CTL and antibody epitope motifs therein, and the importance of the elevation and specificity of PSCA expression in the subject cancers. Applicants argue that with respect to inducing an immune response as in claim 78, the specification also teaches all the steps necessary to induce an immune response against a PSCA protein or fragment thereof. However, the fact that the methods were not actually practiced in subjects with cancer is no bar to enablement (see, *Brana* decision). The use of a GST-PSCA polypeptide conjugate to induce a humoral response in mice without cancer is disclosed in Example 5 at page 89 of the original specification. The epitope domains of PSCA with respect to the various monoclonal antibodies is also disclosed in the paragraph bridging pages 92 and 93.

Applicants' arguments have been carefully considered, but have not been found persuasive because in the absence of a showing that the claimed methods will induce an immune response that will treat cancer the claims are not enabled for the reasons previously set forth.

Applicants argue that, as discussed above, the state of the art is high enough for others in the field to have already begun to practice the claimed invention largely as taught by the

specification (see, above discussion of the Thomas-Kaskel et al., Matsueda et al., and Kiessling et al. art).

Applicants 'arguments have been carefully considered, but have not been found persuasive for the reasons set forth above and previously.

Applicants argue that with respect to antibodies against PSCA antigen in animals with PSCA expressing cancers, Zhang et al. have confirmed that vaccination with a DNA vaccine based on human PSCA and HSP70 adjuvant enhanced the antigen-specific CD8(+) T-cell response and inhibited PSCA(+) Tumor growth in mice. (see, Zhang et al., *J Gene Med.* 9(8):715-26 (2007), enclosed with IDS).

Applicants' arguments have been carefully considered, but have not been found persuasive because the teachings of Zhang et al. are not commensurate in scope with the claimed invention as Zhang et al. is drawn to DNA vectors expressing PSCA and PSCA-HSP conjugates and are not treating with the proteins as claimed. Furthermore, it is noted Zhang et al. teaches that the PSCA alone vectors have little effect on tumor growth or survival of mice bearing PSCA expressing tumors, see figure 8, p. 723. Thus, assuming that the PSCA expressing from the DNA vector acts as a PSCA administered to a subject to elicit an immune response, as Applicants appear to be assuming, Zhang et al. demonstrates that PSCA alone is ineffective for cancer treatment.

Applicants argue that no art is without its uncertainty. However, the results achieved by Thomas-Kaskel et al., Matsueda et al., Kiessling et al., and Zhang et al. show that the uncertainties posed by the Examiner were no bar to others' practice of the Applicants' methods. In particular, as discussed above, the existence of clinical studies in and of itself is strong evidence that persons in the field consider the uncertainty in the art to be acceptably low. Applicants argue that the quantity of experimentation necessary to practice the invention with exemplified and non-exemplified aspects appears to be well within what is routinely performed by a person of ordinary skill in the art of therapeutics development. Applicants argue that as set forth in the MPEP §2164.01 (a), the final step in making the determination that "undue experimentation" would have been needed to make and use the

claimed invention is reached by weighing all the above noted factual considerations. *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 737." Considering all the above, the simple fact is *that persons in the art are using the claimed invention successfully with no sign of undue experimentation.*

Applicants' arguments have been carefully considered, but have not been found persuasive because Applicants are reiterating arguments set forth above, thus for the reasons set forth above and previously undue experimentation would be required to practice the claimed methods.

In the remarks of June 27, 2008 Applicants argue:

Applicants argue that in an earnest attempt to expedite prosecution and without acquiescing on the merits of the rejection, Applicants have amended independent claims 53 and 78 to set forth the embodiment wherein dendritic cells are used to present PSCA the protein or protein fragments to T cells in the context of MHC class I and II molecules.

Applicants argue that as outlined in Applicant's previous response, submitted on October 11, 2007 and herein incorporated by reference, the existence of clinical trials strongly evidences that persons of ordinary skill in the art felt the art was reasonably predictable and ought to be so viewed by the Examiner. Indeed, the MPEP §2107.03 at 2100-35 right column provides

... In order to determine a protocol for phase I testing, the first phase of clinical investigation, some credible rationale of how the drug might be effective or could be effective would be necessary. Thus, as a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.

[underlining in the original].

Applicants argue that Thomas-Kaskel et al. (already of record) have reported the results of a clinical trial using PSCA 14-22 and PSA peptide-loaded dendritic cells to vaccinate advanced prostate cancer patients (see. Thomas-Kaskel et al., Intl. J. Cancer 119:2428-2434 (2006), already of record). The study concludes:

> The experience from this trial argues that DC-based vaccination against PSCA in the dose range given seems worthwhile for further clinical testing as a vaccination antigen. However, immunosuppression is likely to prevent higher rates of immune responders unless active immunotherapy is being employed earlier in the course of the disease, for example in the setting of a "PSA relapse" after radical prostatectomy. The correlation of immune responses with superior overall survival, further supported by documented regression of lymph node metastasis or impressive subjective pain relief, suggests that tumor-specific cellular immunity may indeed provide clinical benefit in CaP, although the optimal time point and vaccination schedule need further clarification.

Applicants argue that considering the above, persons in the art are using the claimed invention successfully with no sign of undue experimentation. Thus, the claims are clearly enabled.

Applicants' arguments have been carefully considered, but have not been found persuasive. Although the teachings of Thomas-Kaskel et al. are enabling for the PSCA 14-22 peptide-loaded dendritic cells, given that the claims are drawn to numerous PSCA immunogenic fragments other than PSCA 14-22 and given the unpredictability in the art of peptide immunotherapy and the identification of peptides that will function as claimed, undue

experimentation would be required for one of skill in the art to predictably make and use the invention as claimed for the reasons previously set forth.

Applicant's arguments have not been found persuasive and the rejection is maintained.

4. All other objections and rejections recited in the Office action of December 28, 2007 are withdrawn.

5. No claims allowed.

6. This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed. The Notice of Appeal must be accompanied by the required appeal fee.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal form, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice

of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/

Examiner, Art Unit 1642

/PJR/

/Karen A Canella/

Primary Examiner, Art Unit 1643